Management and Significance of Synchronous Colorectal Neoplasms in Surgically Treated Gastric Cancer Patients

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Abstract

Background: The existence of other primary tumors during the treatment and management of gastric cancer (GC) is an important issue. This study investigated the prevalence and management of synchronous colorectal neoplasms (CRNs) in surgically treated GC patients.

Methods: Of 381 surgically treated GC patients, 332 (87.1%) underwent colonoscopy to detect CRNs before surgery or within a year after surgery.

Results: CRNs were synchronously observed in 140 patients (42.2%). Adenoma was observed in 131 patients (39.4%). Endoscopic resection was performed in 18 patients with adenoma. Colorectal cancer (CRC) was observed in 16 patients (4.8%), superficial CRC in 13 and advanced CRC in 3 patients. Endoscopic resection of superficial CRC was performed in 7 patients, whereas simultaneous surgical resection of CRC was performed in 9 patients. CRNs were more frequently observed in men. CRC was more frequently observed in GC patients with distant metastasis, albeit without significance. The overall survival of GC patients with CRNs or CRC was

poorer than that of patients without CRNs or CRC. Surgically treated GC is frequently associated with synchronous CRNs.

Conclusion: Intensive colonoscopy followed by endoscopic or surgical removal of CRN has a positive influence on long-term patient survival.

Key words: gastric cancer, colonoscopy, colorectal cancer, colorectal adenoma

Introduction

Gastric cancer (GC) associated with other primary cancers (OPCs) has been reported from the viewpoint of investigating the clinicopathological features of this condition and patient outcome[1-6]. The incidence of colorectal cancer (CRC) has been increasing rapidly in recent decades in Asian countries including Japan[7], and CRC is a common OPC in GC patients[1, 3-5]. However, there are only a few reports on the synchronous prevalence of colorectal neoplasms (CRNs), including adenomas and adenocarcinomas, in GC patients screened intensively by colonoscopy before gastrectomy[8-10], and the management and significance of synchronous CRNs is not sufficiently known in surgically treated GC patients thus far. The close relationship between the development of GC and *Helicobacter pylori* (HP) infection is well known[11-13], and it has recently been noted that this bacterial infection increases the risk of CRC[14-16]. Furthermore, the associations of CRNs and CRC with obesity are well known[17-20]. Under these conditions, it may be important to be aware of the prevalence and management of coexisting CRNs in GC patients.

The purpose of the present study was to investigate the prevalence and management of synchronous CRNs detected by colonoscopy in surgically treated GC patients, and the significance of their association in the survival of these patients.

Patients and Methods

Patients and materials

In total, 381 consecutive GC patients who underwent gastrectomy in Shinshu University Hospital between 2002 and 2009 were studied in the present study. The background data of the GC patients examined by colonoscopy are summarized in Table 1. In total, 332 (87.1%) of the 381 GC patients underwent colonoscopy for the detection of CRN before surgery. In the other 49 patients, colonoscopic examination was not performed because of patient refusal or the early recurrence of GC after surgery with/without malignant gastric stenosis before surgery. The removed stomachs were examined by routine histopathological procedures, and the

clinicopathological features of GC were described according to the TMN classification (the 7th Edition). HP infection was also determined in these specimens.

Colonoscopy in GC patients

Generally, colonic lavage was used with 2000 mL of solution containing polyethylene glycol. When preoperative colonoscopy could not be performed because of malignant gastric stenosis, colonoscopy was performed within a year after surgery. Colonoscopy was performed by our group or by endoscopists in Shinshu University Hospital and other hospitals in Nagano Prefecture. These endoscopists were generally Board Certified Fellows of the Japan Gastroenterological Endoscopy Society. When endoscopists did not have such certification, 1 or 2 endoscopists with certification assisted them during the procedure. CRN detected by colonoscopy was histopathologically diagnosed based on the biopsy specimens as follows: colorectal adenomas with low-grade dysplasia (LGD) or high-grade dysplasia (HGD) and carcinoma.

Treatments for CRNs

CRNs detected by colonoscopy before surgery were managed by follow-up or removal according to the histopathological findings of the biopsy specimens. Generally, patients with adenomas with LGD less than 10 mm in diameter were followed up by colonoscopy in the subsequent year, whereas LGD over 10 mm in diameter were removed endoscopically. Adenomas with HGD and mucosal adenocarcinomas were removed endoscopically. When submucosal adenocarcinomas were diagnosed, these tumors were divided into 2 types, slight submucosal invasion (judged as <1,000 μm) and massive submucosal invasion (judged as ≥1,000 μm), on endoscopic ultrasonography. Adenocarcinomas with slight submucosal invasion were removed endoscopically, while those with massive submucosal invasion were removed surgically. CRC with invasion to the proper muscle layer or more was removed surgically.

Statistical analysis

Data are shown as the prevalence or mean value, and continuous data were

analyzed by the Mann-Whitney *U* test. Ordinal data were compared using the χ^2 test. Survival curves after surgery were analyzed employing the Kaplan-Meier method. *p* values <0.05 were considered significant.

Results

CRNs, including adenomas and adenocarcinomas, were synchronously detected in 140 (42.2%) of the 332 patients examined by colonoscopy (Figure 1). Six patients had symptoms, including bloody (but not tarry) stools, caused by CRNs. Eight patients underwent a colorectal resection for antecedent CRC.

In total, 234 synchronous colorectal adenomas were observed in 131 patients (39.4%; Figure 2), i.e., 230 adenomas with LGD in 128 patients and 4 adenomas with HGD in 4 patients. The characteristics of adenomas are shown in Table 2. Endoscopic resection for adenomas was synchronously performed in 18 patients, i.e., 37 adenomas with LGD in 17 patients and 2 adenomas with HGD in 2 patients. The patients with endoscopically

removed CRNs had no complications caused by colonoscopic treatment. Conversely, 16 synchronous colorectal adenocarcinomas were observed in 16 (4.8%) of the 329 patients. The characteristics of these adenocarcinomas are shown in Table 3. Twelve CRCs (75%) were observed in the left colon and rectum. Seven superficial adenocarcinomas were endoscopically removed prior to gastrectomy, and 9 CRCs were simultaneously removed surgically. The patients with surgically removed CRC had no complications caused by colorectal surgery.

The clinicopathological features of patients with GC associated and unassociated with CRNs are shown in Table 4. Synchronous CRNs were more frequently observed in men than in women ($p = 0.006$) and in patients with smoking habits ($p = 0.005$). Total gastrectomy was frequently performed in GC patients with CRNs ($p = 0.049$); however, there was no difference in the other clinicopathological features, including the incidence of HP infection and body mass index (BMI), between patients with and without CRNs. In multivariate analysis, smoking was an independent risk factor for the

presence of CRNs in GC patients (p = 0.049; odds ratio, 0.618; 95% confidence interval, 0.3827–0.9979), whereas the male gender tended to be an independent risk factor for the presence of CRNs in GC patients (p = 0.054; odds ratio, 1.713; 95% confidence interval, 0.9911–2.9605).

The clinicopathological features of patients with GC associated and unassociated with synchronous CRCs are shown in Table 5. In GC patients with CRCs, distant metastasis was frequently observed (p = 0.08), albeit without significance. There was no difference in clinicopathological features between patients with and without CRNs.

The overall survival after surgery in the patients with CRNs was poorer than that in patients without CRNs (p = 0.033; Figure 3-A); the overall survival in patients with CRCs was also poorer than that in patients without it (p = 0.049; Figure 3-B). However, in Cox's proportional hazard test, CRNs and CRC were not independent factors for survival, although older age, absence of HP infection, advanced GC, and node metastasis were independent factors for long-term patient survival after gastrectomy (Table

6).

Discussion

Regarding synchronous OPC in GC patients, previous reports indicated that the most frequently concurrent OPC was CRC, but it was present in only 1% of GC patients. Regarding synchronous CRC screened by colonoscopy in GC patients, previous reports indicated that CRC was observed in 2%–4% of GC patients, and colorectal adenoma was observed in 30%–40% of these patients[8-9]. The present study demonstrated that the concurrence rate of CRC was 4.8% and that of adenoma was 37.3%. These findings were similar to the previous results obtained via intensive check-ups using colonoscopy in GC patients treated with gastrectomy; however, these rates in previous reports were more than 2-fold different between GC patients who underwent intensive screening of the colon and those who did not undergo this intensive training. Our results regarding the prevalence of CRNs detected by colonoscopy before surgery are considered precise because the patients were

recruited consecutively. Furthermore, Joo et al.[21] reported that endoscopists should perform routine colonoscopy in patients who underwent endoscopic removal of gastric neoplasms, including adenoma and early GC, because of their high prevalence. Yang et al.[22] also reported that the risk of colorectal adenoma was higher in patients with gastric adenoma. Therefore, in GC patients scheduled for elective gastrectomy, it is necessary to perform colonoscopy to detect CRN.

There were a few limitations to this examination of the lower digestive tract. Locally advanced GC located in the pylorus and cardia of the stomach frequently exhibited malignant stenosis. The preparation of colonic lavage using massive amounts of solution may be frequently difficult in these GC patients before surgery. In the present study, 12.9% of the surgically treated GC patients could not be examined by colonoscopy, although other reports revealed no precise data on this issue. Saito et al.[8] reported the prevalence of CRNs screened by colonoscopy based on data in which 433 of 899 GC patients were excluded. Kim et al.[9] reported the prevalence of CRNs in

consecutive GC patients screened by colonoscopy, but the number of GC patients who were excluded was not known. Advanced GC is a malignancy with a poor prognosis, and it occasionally displays early recurrence and metastasis, including peritoneal dissemination, after surgery. Although colonoscopic examination may be scheduled after surgery because of malignant stenosis, colonoscopy may not be possible to perform in gastrectomized patients with early recurrence and metastasis.

Regarding the management and treatment of CRC synchronously associated with GC, CRCs were endoscopically removed before gastrectomy or surgically removed concomitantly in the present study. Because there was no complication caused by CRC treatment in these patients with CRC, synchronous CRC in GC patients can be simultaneously treated by surgery or endoscopy. However, the histological findings of superficial adenocarcinomas endoscopically treated before gastrectomy have to attend for further treatment of them. Eom et al.[6] also discussed combined surgical resection for both GC and CRC. Successful surgical and endoscopic

management for GC patients with CRC necessitates an intensive examination for CRC before surgery using colonoscopy in GC patients. However, colorectal adenoma is a premalignant lesion, and this histological grading is a good indication for endoscopic removal. In GC patients who undergo gastrectomy, adenoma with HGD is associated with adenocarcinoma; therefore, it is necessary to remove the lesion endoscopically. Although 17.1% of adenomas were removed in the present study, these treatments for non-small cell adenoma with LGD may be able to prevent subsequent CRC in gastrectomized patients. Long-term results in these patients are necessary for comparisons with other data without endoscopic treatment or intensive examination of the lower digestive tract.

Regarding the incidence of HP infection, we found no difference between GC patients with and without CRNs/CRC, although several previous studies revealed a positive correlation between HP infection and CRNs/CRC[14-16]. Because our data examined gastrectomized patients with GC, the enrolled patients had a high prevalence of HP infection. In this situation,

it is difficult to ascertain the association between CRNs/CRC and HP infection. Furthermore, regarding obesity as evaluated by the BMI, we found no difference between GC patients with and without CRNs or CRC, although many previous studies reported a positive correlation between BMI and CRN/CRC[17-20]. Kim et al.[9] also reported that BMI did not significantly affect the incidence of CRN in GC patients. Because our data examined GC patients who underwent elective gastrectomy, these patients occasionally displayed body weight loss caused by GC. Thus, it was difficult to clarify the association between CRNs/CRC and obesity.

In the present study, smoking was an independent risk factor for the presence of CRNs in GC patients. Although smoking was not an independent prognostic factor, numerous studies demonstrated that smoking increases the risk for CRNs, and it was significantly associated with CRC incidence and mortality[23, 24]. Samadder et al.[25] reported differential associations between cigarette smoking and CRC subtypes defined by *KRAS* mutation status, and these associations are consistent with the hypothesis that

smoking adversely affects the serrated pathway of colorectal carcinogenesis among older women[24]. Therefore, more careful colonoscopy is required for GC patients with smoking habits.

To our knowledge, there is no report on the long-term outcome of GC patients with CRNs including colorectal adenoma, although there are many reports regarding that with CRC. Our study revealed a poor outcome after surgery. However, this association is not an independent prognostic factor. Advanced GC with node metastasis is associated with a poor prognosis; however, the clinical outcome has recently been improved using several modalities including endoscopic treatment, surgery, and chemotherapy. In this situation, it is important to evaluate the presence of other neoplasms including CRNs/CRC to further improve the long-term outcome of GC patients. We failed to reveal CRNs/CRC as independent prognostic factors in gastrectomized patients because CRNs and CRC were examined and managed intensively by colonoscopy before surgery.

In conclusion, GC in patients, especially men eligible for surgical

treatment, is frequently associated with synchronous CRNs, including CRC. Intensive examination by colonoscopy followed by endoscopic or surgical removal of CRNs and CRC has a positive influence on the long-term survival of patients.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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Table 1.
Background data of 332 gastric cancer patients.

Age (years old; mean±SD)	67.1±10.1
Gender	
men	242 (72.9%)
women	90 (27.1%)
Smoking	123
Drinking	146
Body mass index	22.6±3.4
Tumor site	
upper stomach	105 (31.6%)
middle stomach	125 (37.7%)
lower stomach	102 (30.7%)
Mean tumor size (mm; range)	49.9 (3-175)
Histologic type	
well/moderately differentiated	193 (58.1%)
poorly differentiated/signet ring cell	128 (38.6%)
others*	11 (3.3%)
Depth of invasion	
pT1	176 (53.0%)
pT2 and more	156 (47.0%)
Node metastais	
pN0	190 (57.2%)
pN1 or more	142 (42.8%)
Distant metastasis	
M0	297 (89.5%)
M1	35 (10.5%)
pStage	
I	183 (55.1%)

II	56 (16.9%)
III	58 (17.5%)
IV	35 (10.5%)
Surgical procedures	
total gastrectomy	127 (38.3%)
distal gastrectomy	171 (51.5%)
proximal gastrectomy	20 (6.0%)
partial gastrectomy and others**	14 (4.2%)
Helicobacter pylori infection	
with	303 (91.3%)
without	29 (8.7%)
Surgical mortality	0

*, including neuroendocrine carcinoma and hepatoid carcinoma.

**, including gastorojejunostomy, gastrostomy and exploratory laparotomy.

Table 2.
Clinicopathologic features of colorectal adenomas detected by colonoscopy.

Number of cases with adenoma	131
Number of adenomas	234
Age (years old; mean±SD)	68.3±8.3
Gender	
men	106 (80.9%)
women	25 (19.1%)
Tumor site	
right colon	54 (23.1%)
transverse colon	48 (20.5%)
left colon	108 (46.2%)
rectum	24 (10.3%)
Mean tumor size (mm; range)	5.3 (2-46)
Histologic grading	
low-grade dysplasia	230 (98.3%)
high-grade dysplasia	4 (1.7%)

Table 3.
Clinicopathologic features of colorectal cancer detected by colonoscopy.

Number of cases with cancer	16
Number of cancers	16
Age (years old; mean±SD)	68.2±8.3
Gender	
men	13 (81.3%)
women	3 (18.7%)
Tumor site	
right colon	1 (6.2%)
transverse colon	3 (18.8%)
left colon	7 (43.8%)
rectum	5 (31.2%)
Mean tumor size (mm; range)	19.3 (10-45)
Histologic type	
well-moderately	16 (100%)
poorly	0 (0%)
Depth of invasion	
pT1	13 (81.3%)
pT2 or more	3 (18.7%)
Node metastais	
pN0	14 (87.5%)
pN 1or more	2 (12.5%)
Distant metastasis	
M0	16 (100%)
M1	0 (0%)

Table 4.
Clinicopathologic features of gastric cancer with and without colorectal neoplasm.

Variable	With neoplasm (n=140)	Without neoplasm (n=192)	*p* -value
Age (years old; mean±SD)	68.3±8.3	66.7±11.2	0.16
Gender			
men	113	129	0.006
women	27	63	
Somoking	64	59	0.005
Dinking	66	80	0.32
Body mass index	22.8±3.8	22.4±3.1	0.36
Tumor site			
upper stomach	46	59	0.6
middle stomach	53	72	
lower stomach	41	61	
Tumor size (mm; mean±SD)	47.4±33.5	53.3±37.9	0.13
Histologic type			0.46
well/moderately	85	108	
poorly/signet ring cell	50	78	
others	5	6	
Depth of invasion			0.66
pT1	72	104	
pT2 and more	68	88	
Node metastais			0.5
pN0	77	113	
pN1 or more	63	79	
Distant metastasis			0.47
M0	123	174	

M1	17	18	
TNM staging			0.37
I	73	110	
II	26	30	
III	24	34	
IV	17	18	
Multiple gastric cancers			0.78
with	14	21	
without	126	171	
Surgical procedures			0.049
total gastrectomy	61	66	
distal gastrectomy	66	105	
proximal gastrectomy	6	16	
partial gastrectomy and others*	7	7	
Helicobacter pylori infection			>0.99
with	128	175	
without	12	17	

SD, standard deviation

*, including gastorojejunostomy, gastrostomy and exploratory laparotomy.

Table 5.
Clinicopathologic features of gastric cancer with and without colorectal cancer.

Variable	With cancer (n=16)	Without cancer (n=316)	*p*-value
Mean age (years old; mean±SD)	67.3±10.2	68.2±8.3	0.73
Gender			
men	13	229	0.57
women	3	87	
Smoking	5	118	0.62
Drinking	6	140	0.59
Body mass index	23.3±3.5	22.5±3.4	0.35
Tumor site			0.78
upper stomach	6	99	
middle stomach	5	120	
lower stomach	5	97	
Tumor size (mm; mean±SD)	49.2±34.7	63.4±47.6	0.12
Histologic type			0.22
well/moderately	12	181	
poorly/signet ring cell	3	125	
others	1	10	
Depth of invasion			0.46
pT1	7	169	
pT2 and more	9	147	
Node metastais			>0.99
pN0	9	181	
pN1 or more	7	135	
Distant metastasis			0.08
M0	12	285	

M1	4	31	
TNM staging			0.17
I	7	176	
II	2	54	
III	3	55	
IV	4	31	
Multiple gastric cancers			0.16
with	0	35	
without	16	281	
Surgical procedures			0.25
total gastrectomy	9	118	
distal gastrectomy	5	166	
proximal gastrectomy	1	19	
partial gastrectomy and others*	1	13	
Helicobacter pylori infection			0.15
with	13	290	
without	3	26	

SD, standard deviation

*, including gastorojejunostomy, gastrostomy and exploratory laparotomy.

Table 6. Multivariate analysis for survivals.

Variable	Hazard ratio	95% confidence interval	*p* -value
Colorectal neoplasm	1.4920	0.7178 - 3.1014	0.2838
Colorectal cancer	1.4382	0.9680 - 2.1367	0.0720
Gender	0.6936	0.4306 - 1.1172	0.1325
Age (70 year-old)	1.8284	1.2353 - 2.7064	0.0026
Depth of invasion (pT1 vs. pT2 or more)	2.2104	1.0361 - 4.7155	0.0402
Node metastasis (pN0 vs. pN1 or more)	2.5851	1.3964 - 4.7854	0.0025
Stage (I vs. II or more)	1.5492	0.6246 - 3.8423	0.3449
Helicobacter pylori infection	0.4971	0.2773 - 0.8912	0.0189

Figure legends

Fig. 1. Number of gastric cancer patients with colorectal neoplasms

Synchronous colorectal neoplasms were detected in 332 of 381 surgically treated gastric cancer patients.

*, percentage of patients was calculated using the 332 patients who underwent colonoscopy.

LGD, low-grade dysplasia; HGD, high-grade dysplasia.

Fig. 2. Number of synchronous colorectal neoplasms in gastric cancer patients

Among 250 synchronous colorectal neoplasms, 16 cancers and 234 adenomas were observed in 16 and 234 patients, respectively.

LGD, low-grade dysplasia; HGD, high-grade dysplasia.

Fig. 3. Survival curves of gastric cancer patients

A. Colorectal neoplasms. There was a significant difference in the overall

survival after gastrectomy between patients with and without colorectal neoplasms ($p = 0.033$).

B. Colorectal cancer. There was a significant difference in the overall survival after gastrectomy between patients with and without colorectal cancer ($p = 0.049$).

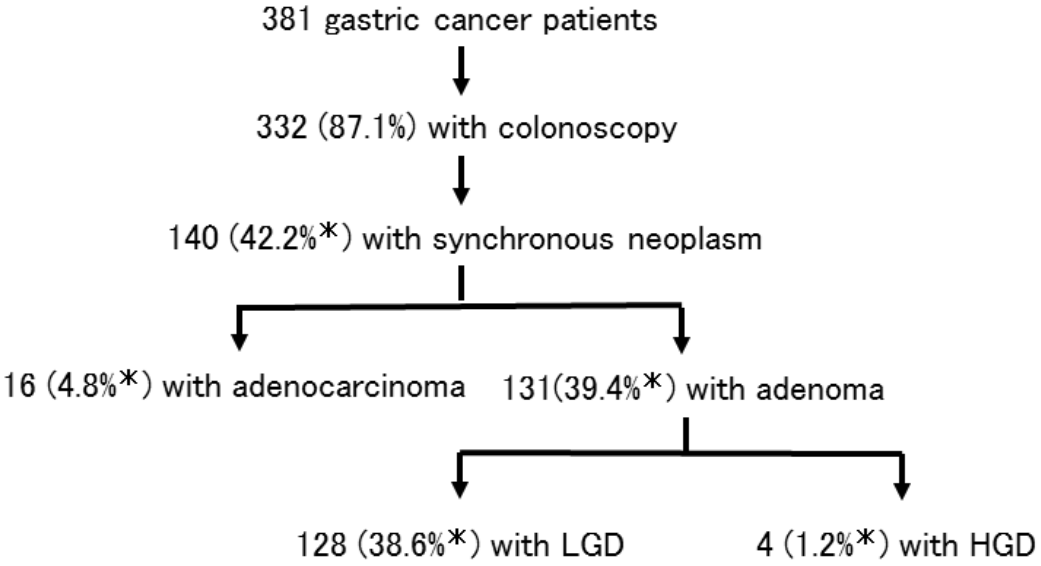


Figure 1

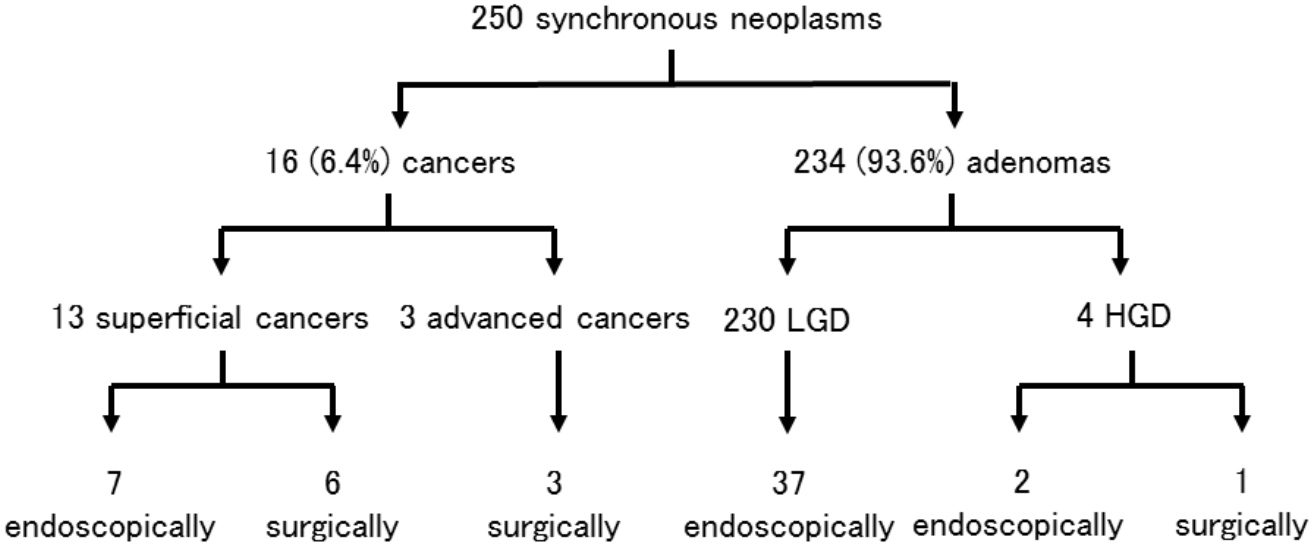
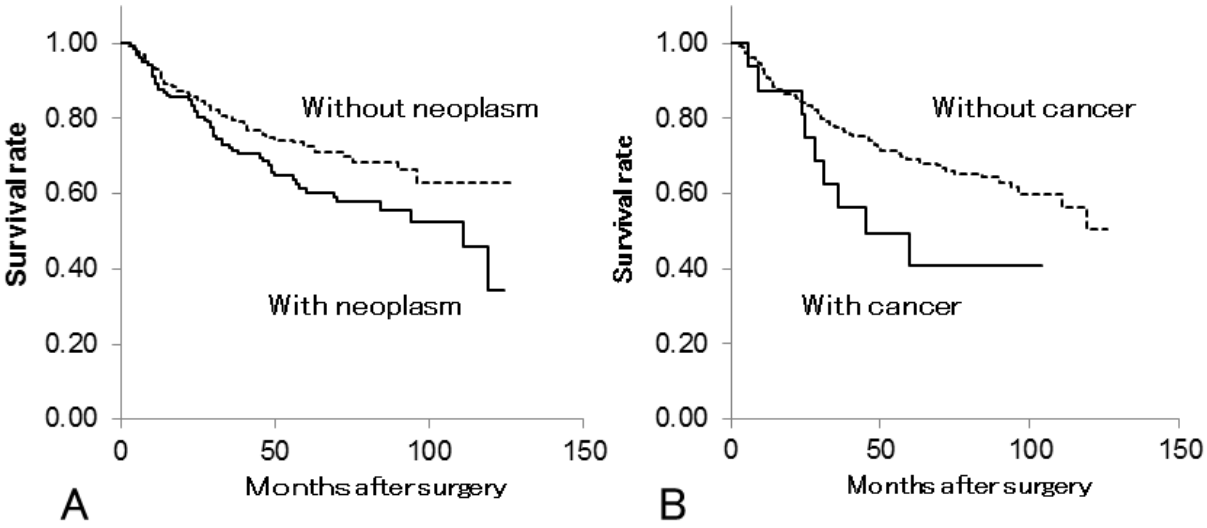


Figure 2


1.00
0.80
0.60
0.40
0.20
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Survival rate
Without neoplasm
With neoplasm
0
50
100
150
Months after surgery
A
1.00
0.80
0.60
0.40
0.20
0.00
Survival rate
Without cancer
With cancer
0
50
100
150
Months after surgery
B

Figure 3